REMARKS

Claims 5, 8-21 and 74-82 are now pending in this application. Claims 5, 8, 13-17 and 74 are currently amended, and claims 1-4, 6-7 and 22-73 are cancelled without prejudice or disclaimer of any previously claimed subject matter. Claims 76-82 are new. The claims have been amended to include β-L-2'-deoxy nucleosides with only cytosine or thymidine bases. The Examiner has withdrawn claims 26-73 from consideration. The Examiner has also withdrawn from consideration, the portion of claims 1-5 wherein X is SO_2 or CH_2. The pending claims have been amended to remove these embodiments.

Rejections under 35 USC § 112

The Examiner has rejected prior pending claims 1-25 and 74-75 under 35 USC § 112 as indefinite. The Examiner states that the claims are drawn to methods of treating a host infected with a drug-resistant form of HBV by administering β-L-2'-deoxynucleosides, but the claims do not recite to whom the nucleosides are to be administered. Claims 1-4 and 22-25 have been cancelled and independent claims 5, 8 and 13-17 have been amended to recite that the β-L-2'-deoxynucleosides are to be administered to the host. Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC § 103

The Examiner has rejected claims 1-25 and 74-75 as obvious over U.S. Patent No. 6,395,716 to Gosselin *et al.* ("Gosselin") in view of U.S. Patent No. 6,855,346 B2 to Wu ("Wu"). Gosselin discloses methods of treating a host infected with hepatitis B virus (HBV) by

administering the disclosed 2'-deoxy-β-L-nucleosides to the host. Gosselin discloses in column 12, lines 39-50 that

> The anti-hepatitis B viral activity of β-L-2'-dA, β-L-2'-dC, β-L-2'-dU, β-L-2'-dG, β-L-2'-dT, β-L-dI, or other β-L-2'-nucleosides provided herein, or the prodrugs, phosphates, or salts of these compounds, can be enhanced by administering two or more of these nucleosides in combination or alternation. Alternatively, for example, one or more of β-L-2'-dA, β-L-2'-dC, β-L-2'-dU, β-L-2'-dG, β-L-2'-dT, β-L-dI, or other β-L-2'-nucleosides provided herein can be administered in combination or alternation with 3TC, FTC, L-FMAU, DAPD, famciclovir, penciclovir, BMS-200475, bis pom PMEA (adefovir, dipivoxil); lobucavir, ganciclovir, or ribavarin.

Wu teaches that lamivudine (i.e., 3TC) resistant viruses can have a characteristic amino acid substitution over the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the RNA-dependent DNA polymerase enzyme. Wu teaches that the methionine at codon 552 is replaced by isoleucine or valine. This disclosure is a statement of the scientific knowledge of mutations in lamivudine-resistant HBV. Wu does not disclose that β-L-2'-deoxythymidine (L-dT) or β-L-2'deoxycytidine (L-dC) are useful for the treatment of HBV that contains a mutation at the 552 codon of HBV. Wu discloses a method of treatment of HBV infections by administering a combination of lamivudine and a pharmaceutical composition named "YGK", comprising aqueous extracts of various herbs.

While Gosselin refers to the use of LdT or LdC in combination with 3TC, the patent did not specifically address what happens when hepatitis B becomes resistant to 3TC. The presently claimed invention is not obvious because as of the filing date, it had been published that HBV strains that are resistant to 3TC (lamivudine) are also resistant to L-dT and L-dC, and therefore, neither L-dT nor L-dC should be used to treat patients with lamivudine-resistant hepatitis B.

Specifically, the present application was filed on September 15, 2003, claiming priority to provisional application No. 60/410,675, filed on September 12, 2002. As disclosed in the specification on page 4, paragraph 51, and in citation DI of the Information Disclosure Statement filed March 2, 2004, an oral presentation by William E. Delaney at the European Association for the Study of the Liver meeting in Madrid Spain on April 17-21, 2002 disclosed that lamivudine-resistant HBV with a mutation at the L528M or M552I or with a double mutation at L528M and M552V are cross-resistant to L-dT (β-L-2'-deoxythymidine) *in vitro*. Abstract # 1825 of the presentation discloses that the mutations confer a high degree of resistance to lamivudine (> 1000 fold increase in IC50 values), and that the M552I mutation and the L528M + M552V double mutation also conferred a cross-resistance to L-dT. IC_{50} values for L-dT increased > 235 and > 132 fold, with HBV containing the M552I and L528M + M552V mutations, respectively. This disclosure presents a convincing argument that L-dT would not be useful for the treatment of lamivudine-resistant HBV.

An additional publication by Delaney *et al.* (Delaney, W. *et al.* J. Hepatology, 2002; 36 (suppl. 1):89, abstract # 309) discloses that HBV with the mutation rtM204I (M522I) or the double mutation rtL180M (L528M) + rtM204V (M552V) in the viral polymerase confers resistance to L-dC and L-dT. A copy of this abstract is enclosed. This publication discloses that the rtL180M (L528M) mutation conferred an approximately 10-fold resistance to both L-dC and L-dT. The mutation rtM204I (M522I) and the double mutation rtL180m (L528M) + rtM204V (M552V) conferred high levels of resistance to L-dC and L-dT (> 300 fold).

The present claims are based on the discovery that while L-dT and L-dC are cross resistant to lamivudine resistant strains of HBV that carry the M522I and L528M mutations and the (M552V + L528M) double mutation, L-dT and L-dC are very active against the important single M552V HBV mutant. This discovery is very important because the M552V single mutant typically appears 4 to 8 weeks prior to the emergence of the highly resistant L515M (also called L528M) + M552V double mutant which reportedly accounts for 60-70% of all lamivudine resistance in hepatitis B patients (L515M is equivalent to L528M, see p. 66, paragraph 720). Because the M552V mutation appears 4 to 8 weeks prior to the emergence of the L515(L528M) + M552V mutation, L-dT and L-dC will exhibit high activity and therapeutic effect within that window to treat the disease, before the virus has further mutated to the double mutant. This

discovery is contrary to the prior published work that did not look at the sensitivity of M552V HBV mutants to L-dT or L-dC, and erroneously suggested that L-dT and L-dC should not be used to treat lamivudine-resistant HBV strains.

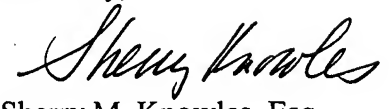
The specification discloses that both L-dT and L-dC demonstrates strong anti-viral activity against HBV with the M552V mutation (see page 69, paragraph 785). Table 24b on page 70 shows that the IC_{50} values for L-dT and L-dC were not significantly altered when measured in a cell line containing the M552V mutation (V1/C9), while lamivudine exhibited a 24.8-fold decrease in IC_{50} with this cell line. L-dT and L-dC did not show improved efficacy compared to lamivudine for cell lines that contained the M552I mutation or the double mutations of L515M + M552V (equivalent to L528M + M552V, see page 4 paragraph 51) or L515M + M552I (equivalent to L528M + M552I, see page 4, paragraph 51). This finding is consistent with the disclosures of Delaney *et al.* The specification discloses that the M552V mutation is critical for the development of lamivudine resistance (page 69, paragraph 785) since it is thought that this is the first step in the pathway that leads to the M515L + M552V double mutant that is responsible for 60-70% of lamivudine resistant forms of HBV. The specification discloses that activity against the key M552V mutation may help to suppress the emergence of viral resistance in patients treated with L-dT.

In summary, the use of β-L-2'-deoxycytidine or β-L-2'-deoxythimidine or their salts or esters or prodrugs for the treatment of a host infected with HBV that exhibits a mutation at the 552 codon from methionine to valine in the DNA polymerase region, as recited in the claims, would not have been obvious in view of Gosselin and Wu because the prior publications of Delaney *et al.* [*Hepatology*, 34(no.4, pt.2): 628A, abstract #1825(2001) and *Hepatology*, 36(suppl. 1): abstract # 309 (2002)] teach away from the claimed invention.

For the Examiner's information, Applicants also enclose a report by assignee Idenix Pharmaceuticals, Inc., which further elaborates on the invention. Withdrawal of the rejection is respectfully requested.

The Commissioner is authorized to charge any fee associated with this Amendment, as well as any other deficiency, to Deposit Account 11-0980.

Sincerely,



Sherry M. Knowles, Esq.
Registration No. 33,052

June 14, 2006
King & Spalding LLP
1180 Peachtree Street
Atlanta, Georgia 30309
404-572-3541 (Direct Line)
404-572-5134 (Facsimile)